Paul Sedaliotz

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

9826

SEARCH REQUEST FORM

1755 661

Requestor's Name: Rebecca Hoist

Serial Number: 10/068 035

Date: 6/23/04

Phone: ~~306~~ Rem 4C70

Art Unit: 1614

mg

Search Topic: Inv. Andrew Stoll

Please provide a updated structure of claim 10 search
it to treat bipolar disorder. It includes
phosphatidylcholine (ie claims 18 & 19
preferred ω-3 fatty acids are
eicosapentanoic acid
docosahexanoic acid
Provide 2 references older than 2/25/99 for
method of treating bipolar disorder with lithium

Thanks
Rebecca

STAFF USE ONLY

Date completed: _____

Searcher: _____

Terminal time: _____

Elapsed time: _____

CPU time: _____

Total time: _____ 20

Number of Searches: _____ 4/2

Number of Databases: _____

Search Site

_____ STIC

_____ CM-1

_____ Pre-S

Type of Search

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

_____ Bibliographic

Vendors

_____ IG

7/14,54 STN

_____ Dialog

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_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

PTO-1590 (9-90)

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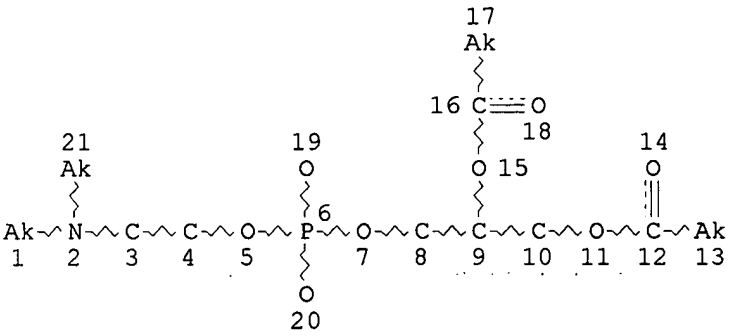


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GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
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L16            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND L15
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↑ general frame work of Phosphatidylcholine

```
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L16  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1997:717821  HCAPLUS
DOCUMENT NUMBER:          128:7311
TITLE:                    Fatty acids and phosphatidylcholines in the treatment
                          of bipolar disorder
INVENTOR(S):              Stoll, Andrew L.; Severus, Wolfram E.
PATENT ASSIGNEE(S):       Brigham and Women's Hospital, USA; Stoll, Andrew L.;
                          Severus, Wolfram E.
SOURCE:                   PCT Int. Appl., 13 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9739759	A2	19971030	WO 1997-US6712	19970423
WO 9739759	A3	19980115		
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9727384	A1	19971112	AU 1997-27384	19970423
US 6344482	B1	20020205	US 1999-269361	19990322
US 2002091103	A1	20020711	US 2002-68035	20020205
US 2003012827	A1	20030116	US 2002-83913	20020227

PRIORITY APPLN. INFO.: US 1996-16140P P 19960424
WO 1997-US6712 W 19970423
US 1999-269361 A1 19990322

AB The present invention is directed to a method of treating patients with bipolar disorder by administering ω-3 fatty acids. These may be administered in a substantially purified form, as part of a pharmaceutical composition, or as part of a larger mol., e.g. a triacylglycerol, which releases free fatty acid after ingestion by a patient. The present invention is also directed to triacylglycerols which are esterified at the γ-carbon of glycerol with phosphocholine and at either the α- or β-carbon of glycerol with an ω-3 fatty acid. These ω-3 phosphatidylcholines are also used in the treatment of patients with bipolar disorder.

IC ICM A61K033-14
ICS A61K031-66; A61K031-20

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

IT **Mental disorder**
(**manic bipolar disorder**; ω-3 fatty acids and phosphatidylcholines for treatment of **bipolar disorder**)

IT 6217-54-5, Docosahexaenoic acid 10417-94-4, Eicosapentaenoic acid **87879-23-0 87879-27-4 98819-78-4 198779-10-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ω-3 fatty acids and phosphatidylcholines for treatment of bipolar disorder)

IT **87879-23-0 87879-27-4 98819-78-4 198779-10-1**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ω-3 fatty acids and phosphatidylcholines for treatment of bipolar disorder)

RN 87879-23-0 HCAPLUS

CN 3,5,8-Trioxa-4-phosphatriaconta-12,15,18,21,24,27-hexaen-1-aminium, 4-hydroxy-N,N,N-trimethyl-9-oxo-7-[[[(5Z,8Z,11Z,14Z,17Z)-1-oxo-5,8,11,14,17-eicosapentaenyl]oxy]methyl]-, inner salt, 4-oxide, (12Z,15Z,18Z,21Z,24Z,27Z)- (9CI) (CA INDEX NAME)

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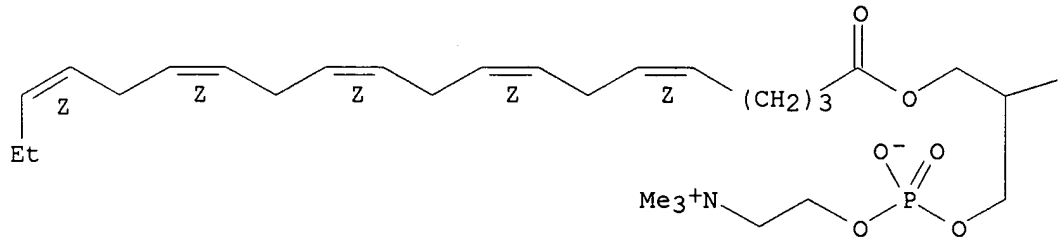

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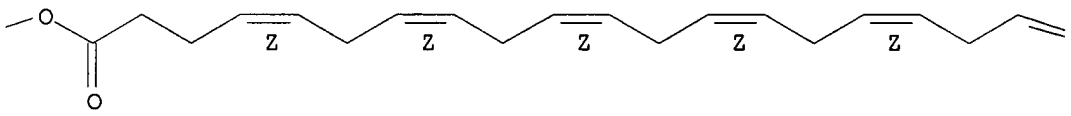

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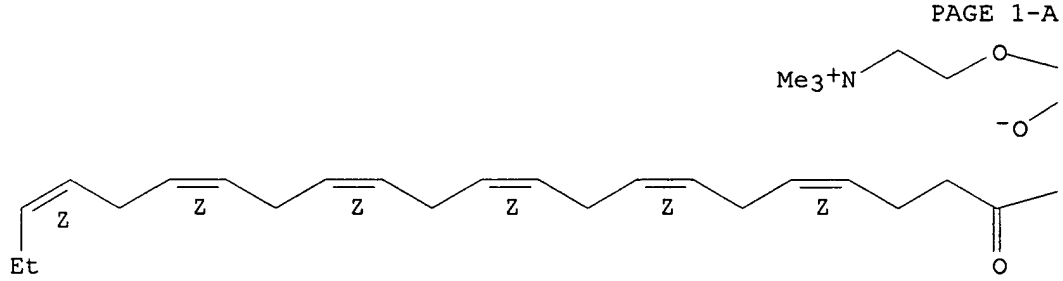

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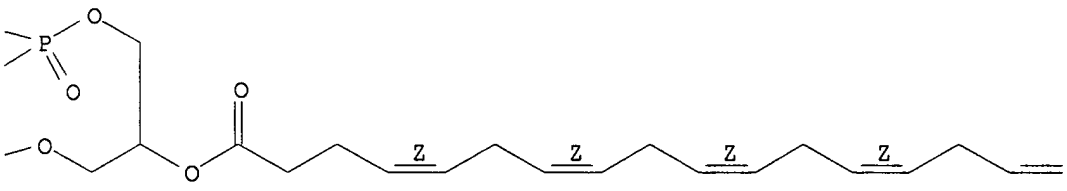

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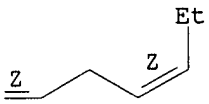

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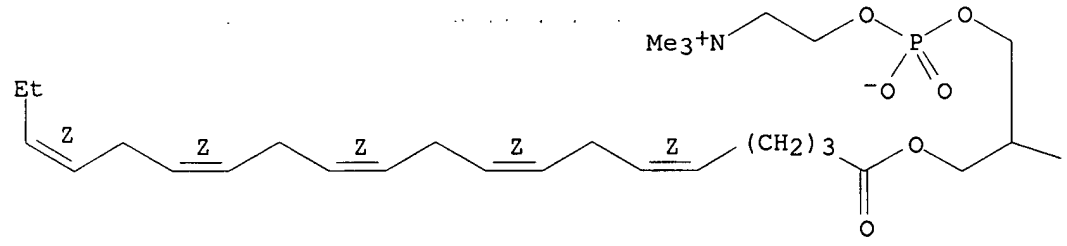
PAGE 1-A



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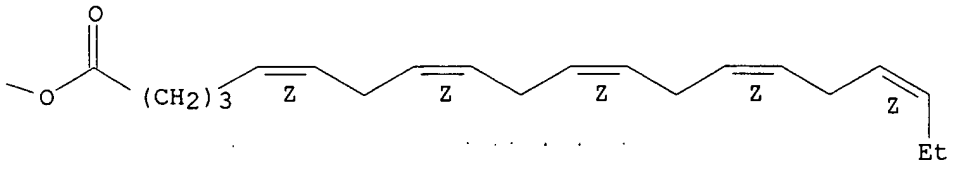

RN 198779-10-1 HCAPLUS

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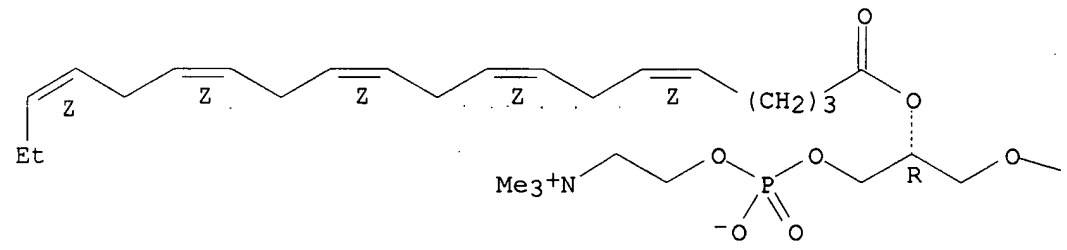
Double bond geometry as shown.

PAGE 1-A



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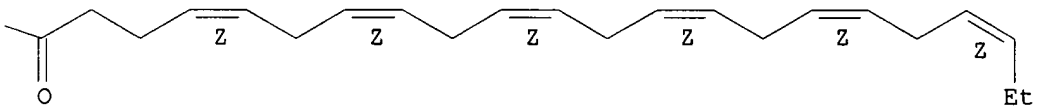

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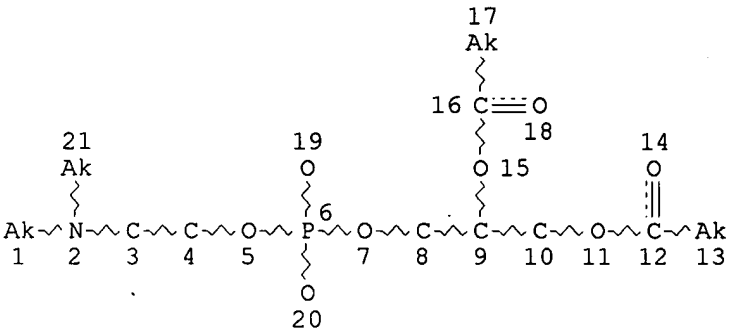


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NODE ATTRIBUTES:
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CONNECT IS E1  RC AT  17
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GGCAT   IS LIN  AT  13
GGCAT   IS LIN  AT  17
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M17-X25 C  AT  13
ECOUNT  IS M17-X25 C  AT  17

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L8          1085 SEA FILE=REGISTRY SSS FUL L6
L9           983 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8/COM
L23          578 SEA FILE=USPATFULL ABB=ON  PLU=ON  L9 OR (PHOSPHATIDYL CHOLIN?
                 OR PHOSPHATIDYLCHOLIN? OR LECITHIN)(3A)"Ω-3"
L25            3 SEA FILE=USPATFULL ABB=ON  PLU=ON  L23 AND BIPOL?(3A)(DISORD?
                 OR MENTAL? OR DISEAS? OR DEMENT?)


=> d l25 bib ab kwic 1-3

L25  ANSWER 1 OF 3  USPATFULL on STN
AN     2003:17078  USPATFULL
TI     Omega-3 fatty acids in the treatment of depression
IN     Stoll, Andrew, Lincoln, MA, UNITED STATES
PI     US 2003012827      A1   20030116
AI     US 2002-83913      A1   20020227 (10)
RLI    Continuation-in-part of Ser. No. US 1999-269361, filed on 22 Mar 1999,
       GRANTED, Pat. No. US 6344482 A 371 of International Ser. No. WO
       1997-US6712, filed on 23 Apr 1997, PENDING
DT     Utility
FS     APPLICATION
LREP   Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA,
       02109
CLMN   Number of Claims: 27
ECL    Exemplary Claim: 1
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DRWN No Drawings
LN.CNT 617
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a method of treating patients with major depression by administering omega-3 fatty acids. These may be administered in a substantially purified form, as part of a pharmaceutical composition, or as part of a larger molecule, e.g., a triacylglycerol, which releases free fatty acid after ingestion by a patient.

The present invention is also directed to triacylglycerols which are esterified at the gamma cardon of glycerol to phosphocholine and at either the alpha or beta carbon of glycerol to an omega-3 fatty acid. These "omega-3 phoshatidylcholines" are also used in the treatment of patients with major depression.

PARN [0001] This application is a continuation-in-part of U.S. Patent Application entitled "Omega-3 Fatty Acids and **Omega-3 Phosphatidylcholine** in the Treatment of **Bipolar Disorder**", filed Feb. 5, 2002, using Express Mail No.: ET796587916US, which is a continuation of U.S. Ser. No. 09/269,361, filed Mar.. . .

SUMM . . . elevated mood and energy (mania) is termed "unipolar major depression."However, a sizeable proportion of depressed patients presenting for treatment have **bipolar disorder** (also known as manic depressive illness), where there is a history of mania, or a milder form of mood elevation. . .

SUMM [0005] The present invention is also directed to an **omega-3 phosphatidylcholine** useful in the treatment of unipolar major depression, consisting of glycerol esterified at both its α and β carbons to. . . It is preferred that at least one of the esterified fatty acids be eicosapentanoic acid, docosahexanoic acid, or α-linolenic acid. **Omega-3 phosphatidylcholines** with eicosapentanoic acid esterified to the carbon and docosahexanoic acid esterified to the β carbon, or vice versa, are the. . .

DETD [0011] **Omega-3 phosphatidylcholine**: As used herein the term "**omega-3 phosphatidylcholine**" refers to a triacylglycerol in which the γ carbon of glycerol is esterified to phosphocholine, and at least one of. . .

DETD . . . line of evidence is the strong antidepressant effect of the omega-3 fatty acids observed a recent double-blind, placebo-controlled study in **bipolar disorder** (Stoll A L, et al.: Omega-3 fatty acids in **bipolar disorder**: a preliminary double-blind, placebo-controlled trial. Archives Gen Psychiatry; 1999, 56:407-412). This study is relevant because all compounds with antidepressant effects in **bipolar disorder** will exhibit antidepressant effects in unipolar depression. The final line of evidence involves preliminary uncontrolled open-label clinical studies reporting mood. . . in patients with unipolar depression and other neuropsychiatric disorders (Rudin, 1981; Stoll A L, et al.: Omega-3 fatty acids and **bipolar disorder**: a review. Prostaglandins, Leukotrienes, and Essential Fatty Acids; 1999, 60:329-37).

DETD . . . Baylor College of Medicine, a 2-site study designed to examine the efficacy of omega-3 fatty acids in patients with unstable **bipolar disorder** was performed (Stoll, 1999). The

study was performed to confirm the hypothesis that one could discover new mood agents by. . .

DETD [0039] D. **Omega-3 Phosphatidylcholines**

DETD [0040] The present invention is also directed to **omega-3 phosphatidylcholines** in which glycerol is esterified at its γ carbon to phosphocholine and at least one of the fatty acids esterified. . .

DETD . . . standard techniques well known in the art, see e.g. U.S. Pat. No. 4,701,468. One suitable method is to synthesize the "**omega-3 phosphatidylcholines**" from commercially available precursor lyso-phosphatidylcholines. Specifically, a lyso-phosphatidylcholine is acylated by combining the desired omega-3 fatty acid anhydride (e.g. from. . . catalyst (1.2 equivalents) in alcohol-free chloroform. Depending on the reaction conditions and the relative proportions of fatty acid, several different **omega-3 phosphatidylcholine** species will be generated. Using EPA and DHA, four major species will occur: dieicosapentanoylphosphatidylcholine, didocosahexanoylphosphatidylcholine, 1-eicosapentanoyl, 2-docosahexanoylphosphatidylcholine, and 1-docosahexanoyl, 2-eicosapentanoylphosphatidylcholine.. . .

DETD [0042] E. Method of Treating **Bipolar Disorder** Using **Omega-3 Phosphatidylcholines**

DETD [0043] The **omega-3 phosphatidylcholines** described above may be used for treating humans with unipolar major depression in the same manner and following the same procedures as those discussed in connection with **omega-3** fatty acids. The **phosphatidylcholines** may be given in a substantially purified form or as part of a pharmaceutical composition. It is expected that optimized dosages will have sufficient **omega-3 phosphatidylcholine** to deliver between about one and about 30 grams of free omega-3 fatty acid per day, with the preferred daily. . .

DETD [0044] As with omega-3 fatty acids, the **omega-3 phosphatidylcholines** may be delivered by any route and are compatible with any dosage form. Oral dosage forms such as tablets, capsules,. . .

DETD [0045] In cases where parenteral administration is elected as the route of administration, preparations containing **omega-3 phosphatidylcholine** may be provided to patients in combination with pharmaceutically acceptable sterile aqueous or non-aqueous solvents, suspensions or emulsions. Examples of. . .

DETD [0046] **Omega-3 phosphatidylcholine** and other psychotropic agents, e.g., lithium, antidepressants, anticonvulsants, mood stabilizers, antipsychotic agents, and beneodiazepines, may be provided as separate components. . .

CLM What is claimed is:

10. An **omega-3 phosphatidylcholine** useful in the treatment of unipolar major depression consisting of glycerol, wherein: a) the α and β carbons of said. . .

11. The **omega-3 phosphatidylcholine** of claim 10, wherein both the α and β carbons of said glycerol are esterified to an omega-3 fatty acid.

. . .

12. The **omega-3 phosphatidylcholine** of either claim 10 or 11, wherein eicosapentanoic acid is esterified to a member of the α carbon, the β. . .

13. The **omega-3 phosphatidylcholine** of

either claim 10 or 11, wherein docosahexanoic acid is esterified to a member of the α carbon, the β. . .
14. The **omega-3 phosphatidylcholine** of either claim 10 or 11, wherein alpha-linolenic acid is esterified to a member of the α carbon, the β. . .
15. The **omega-3 phosphatidylcholine** of claim 10, wherein eicosapentanoic acid is esterified to the α carbon of said glycerol and docosahexanoic acid is esterified. . .
16. The **omega-3 phosphatidylcholine** of claim 10, wherein docosahexanoic acid is esterified to the αcarbon of said glycerol and eicosapentanoic acid is esterified to the β carbon of said **omega-3 phosphatidylcholine**
.

17. A pharmaceutical composition comprising the **omega-3 phosphatidylcholine** of claim 10, wherein one or more unit doses of said composition provides an amount of said **omega-3 phosphatidylcholine** sufficient to reduce or eliminate the symptoms of unipolar major depression.

19. A method of treating unipolar major depression in a human patient, comprising administering the **omega-3 phosphatidylcholine** of claim 10 to said patient at a dose sufficient to reduce or eliminate the symptoms of unipolar major depression.
. . .
. . . kit comprising a carrier containing in close confinement therein, none or more components wherein: a) a first component contains an **omega-3 phosphatidyl-choline;** and
b) a second component contains a psychotropic agent useful in the treatment of unipolar major depression.

IT 463-40-1, α-Linolenic acid 6217-54-5, Docosahexaenoic acid 7439-93-2, Lithium, biological studies 10417-94-4, Eicosapentaenoic acid 12794-10-4D, Benzodiazepine, derivs. **87879-23-0 87879-27-4 98819-78-4 485323-86-2**
(omega-3 fatty acids in treatment of depression)

L25 ANSWER 2 OF 3 USPATFULL on STN
AN 2002:172346 USPATFULL
TI Omega-3 fatty acids and **omega-3 phosphatidylcholine** in the treatment of **bipolar disorder**
IN Stoll, Andrew L., Lincoln, MA, UNITED STATES
Severus, Wolfram E., Berlin, GERMANY, FEDERAL REPUBLIC OF
PI US 2002091103 A1 20020711
AI US 2002-68035 A1 20020205 (10)
RLI Continuation of Ser. No. US 1999-269361, filed on 22 Mar 1999, PATENTED
PRAI WO 1997-US6712 19970423
DT Utility
FS APPLICATION
LREP Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, MA, 02109
CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 439

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to a method of treating patients with **bipolar disorder** by administering omega-3 fatty acids. These may be administered in a substantially purified form, as part of a pharmaceutical composition, or as part of a larger molecule, e.g. a triacylglycerol, which releases free fatty acid after ingestion by a patient.

The present invention is also directed to triacylglycerols which are esterified at the gamma carbon of glycerol to phosphocholine and at either the alpha or beta carbon of glycerol to an omega-3 fatty acid. These "omega-3 phoshatidylcholines" are also used in the treatment of patients with **bipolar disorder**.

TI Omega-3 fatty acids and **omega-3 phosphatidylcholine** in the treatment of **bipolar disorder**

AB The present invention is directed to a method of treating patients with **bipolar disorder** by administering omega-3 fatty acids. These may be administered in a substantially purified form, as part of a pharmaceutical composition,. . .

AB . . . carbon of glycerol to an omega-3 fatty acid. These "omega-3 phoshatidylcholines" are also used in the treatment of patients with **bipolar disorder**.

SUMM . . . to medical treatments for psychiatric disorders. More specifically, it is concerned with novel methods and compositions for treating patients with **bipolar disorder**.

SUMM [0002] Patients with **bipolar disorder** suffer recurrent, alternating cycles of mania and depression. In a controlled clinical study performed more than a decade ago, it. . .

SUMM . . . inhibit thrombosis and platelet aggregation and can lower blood pressure (see Dimmitt, Clin. Exp. Pharmacol. Physiol. 22:204-208 (1995)). Thus, the "**omega-3 phosphatidylcholines**" disclosed herein produce the same effects as lecithin in bipolar patients due to the release of free choline but reduce,. . .

SUMM [0005] In addition, the present invention is directed to a method of treating **bipolar disorder** using omega-3 fatty acids themselves, i.e. apart from phosphatidylcholine. These may be administered in a purified state, as part of. . .

SUMM [0007] Thus, a method has been developed for treating a human patient for **bipolar disorder** by administering omega-3 fatty acids at a dosage sufficient to reduce or eliminate the symptoms associated with the disorder, i.e.. . .

SUMM [0008] The present invention is also directed to an **omega-3 phosphatidylcholine** useful in the treatment of **bipolar disorder**, consisting of glycerol esterified at both its α and β carbons to fatty acids. At least one, and preferably both,. . . phosphocholine. It is preferred that at least one of the esterified fatty acids be either eicosapentanoic acid or docosahexanoic acid. **Omega-3 phosphatidylcholines** with eicosapentanoic acid esterified to the α carbon and docosahexanoic acid esterified to the β carbon and vice versa are. . .

SUMM [0009] In another aspect, the present invention is directed to a pharmaceutical composition comprising one or more of the **omega-3 phosphatidylcholines** discussed above. The composition should contain sufficient triacylglycerol so that one or

more unit doses provides enough agent to reduce or eliminate the symptoms associated with **bipolar disorder**. In some instances, lithium may be also incorporated into the composition in order to improve therapeutic effects.

SUMM [0010] The present invention is also directed to a method for treating **bipolar disorder** in a human patient by administering an **omega-3 phosphatidylcholine**. It is expected that this phosphatidylcholine will typically be administered at a dosage sufficient to provide between 1 and 30. . .

DETD [0013] **Bipolar disorder: Bipolar disorder** refers to a form of psychosis characterized by adnormally severe mood swings. The patient alternates between episodes of mania and. . .

DETD [0017] **Omega-3 phosphatidylcholine**: As used herein the term "**omega-3 phosphatidylcholine**" refers to a triacylglycerol in which the y carbon of glycerol is esterified to phosphocholine and at least one of. . .

DETD [0020] B. Method of Treating Patients For **Bipolar Disorder** Using Omega-3 Fatty Acids

DETD [0021] The present invention is directed to a method for treating human patients for **bipolar disorder** by administering omega-3 fatty acids. Although the method is not restricted to any one particular type of omega-3 fatty acid,. . .

DETD . . . administered to a human patient should be at least the amount required to reduce or eliminate the symptoms associated with **bipolar disorder**. Specifically, the dosage should be high enough to either reduce the severity of the manic and depressive episodes experienced by. . .

DETD . . . patient and other clinically relevant factors. In many cases, a patient will already be taking medications for the treatment of **bipolar disorder** at the time that treatment with omega-3 fatty acid is initiated. In addition, patients may be taking medications for other. . .

DETD . . . composition containing one or more excipients or flavoring agents. Compositions may also include other active ingredients for the treatment of **bipolar disorder**, e.g. lithium. Preparations may be solid or liquid and take any of the pharmaceutical forms presently used in human medicine,. . .

DETD [0033] Omega-3 fatty acids may be used in combination with other agents effective at treating **bipolar disorder**, e.g. lithium or choline. These other agents may either be given together with omega-3 fatty acid in a single dosage. . .

DETD [0036] Individual preparations containing omega-3 fatty acid and other therapeutic agents for **bipolar disorder**, such as choline or lithium, may be provided in the form of a kit, comprising a carrier (e.g. a box. . . one or more components (bottles, vials, packets, etc.) in close confinement. Such a kit will be carried by patients with **bipolar disorder** and will typically contain written instructions concerning the way in which the enclosed drugs should be taken, potential side effects,. . .

DETD [0037] C. **Omega-3 Phosphatidylcholines**

DETD [0038] The present invention is also directed to **omega-3 phosphatidylcholines** in which glycerol is esterified at its γ carbon to phosphocholine and at least one of the fatty acids esterified. . .

DETD . . . standard techniques well known in the art, see e.g. U.S. Pat.

No. 4,701,468. One suitable method is to synthesize the "**omega -3 phosphatidylcholines**" from commercially available precursor lyso-phosphatidylcholines. Specifically, a lyso-phos-phatidylcholine is acylated by combining the desired omega-3 fatty acid anhydride (e.g. from. . . catalyst (1.2 equivalents) in alcohol-free chloroforn. Depending on the reaction conditions and the relative proportions of fatty acid, several different **omega-3 phosphatidylcholine** species will be generated. Using EPA and DHA, four major species will occur: dieicosapentanoylphosphatidylcholine, didocosahexanoylphosphatidylcholin e, 1-eicosapentanoyl, 2-docosahexanoylphosphatidylcholine, and 1-docosahexanoyl, 2-eicosapentanoylphosphatidylcholine.. . .

DETD [0040] D. Method of Treating **Bipolar Disorder** Using Omega-3 Phosphatidyicholines

DETD [0041] The **omega-3 phosphatidylcholines** described above may be used for treating humans with **bipolar disorder** in the same manner and following the same procedures as those discussed in connection with **omega-3** fatty acids. The **phosphatidylcholines** may be given in a substantially purified form or as part of a pharmaceutical composition. It is expected that optimized dosages will have sufficient **omega -3 phosphatidylcholine** to deliver between about one and about 30 grams of free omega-3 fatty acid per day, with the preferred daily. . .

DETD [0042] As with omega-3 fatty acids, the **omega-3 phosphatidylcholines** may be delivered by any route and are compatible with any dosage form. Oral dosage forms such as tablets, capsules,. . . included. It will be appreciated that one particularly attractive composition would include both a source of lithium as well as **omega-3 phosphatidylcholine**.

DETD [0043] In cases where parenteral administration is elected as the route of administration, preparations containing **omega-3 phosphatidylcholine** may be provided to patients in combination with pharmaceutically acceptable sterile aqueous or non-aqueous solvents, suspensions or emulsions. Examples of. . .

DETD [0044] **Omega-3 phosphatidylcholine** and other agents useful in treating bipolar patients, preferably lithium or choline may be provided as separate components in the. . .

CLM What is claimed is:

1. A method of treating a human patient for **bipolar disorder**, comprising administering an omega-3 fatty acid to said patient at a dosage sufficient to reduce or eliminate the symptoms of. . .

10. An **omega-3 phosphatidylcholine** useful in the treatment of **bipolar disorder** consisting of glycerol, wherein: a) the α and β carbons of said glycerol are both esterified to a fatty acid,. . .

11. The **omega-3 phosphatidylcholine** of claim 10, wherein both the α and β carbons of said glycerol are esterified to an omega-3 fatty acid.

. . .

12. The **omega-3 phosphatidylcholines** of either claim 10 or 11, wherein eicosapentanoic acid is esterified to either the α or β carbon of said. . .

13. The **omega-3 phosphatidylcholine** of either claim 10 or 11, wherein docosahexanoic acid is esterified to either the α or β carbon of said. . .

14. The **omega-3 phosphatidylcholine** of claim 10, wherein eicosapentanoic acid is esterified to the α carbon of said glycerol and docosahexanoic acid is esterified. . .
15. The **omega-3 phosphatidylcholine** of claim 10, wherein docosahexanoic acid is esterified to the α carbon of said glycerol and eicosapentanoic acid is esterified to the β carbon of said **omega-3 phosphatidylcholines**.

16. A pharmaceutical composition comprising the **omega-3 phosphatidylcholine** of claim 10, wherein one or more unit doses of said composition provides an amount of said **omega-3 phosphatidylcholine** sufficient to reduce or eliminate the symptoms of said **bipolar disorder**.

18. A method of treating **bipolar disorder** in a human patient, comprising administering the omega-3 phosphatidyicholine of claim 10 to said patient at a dose sufficient to. . .
. . . component contains an omega-3 fatty acid; and b) a second component contains a therapeutic agent useful in the treatment of **bipolar disorder**.

. . . kit comprising a carrier containing in close confinement therein, none or more components wherein: a) a first component contains an **omega-3 phosphatidyl-choline**; and
b) a second component contains a therapeutic agent useful in the treatment of **bipolar disorder**.

IT 6217-54-5, Docosahexaenoic acid 10417-94-4, Eicosapentaenoic acid **87879-23-0 87879-27-4 98819-78-4 198779-10-1**
(ω-3 fatty acids and phosphatidylcholines for treatment of bipolar disorder)

L25 ANSWER 3 OF 3 USPATFULL on STN
AN 2002:24309 USPATFULL
TI Omega-3 fatty acids in the treatment of **bipolar disorder**
IN Stoll, Andrew L., 35 Old Winter St., Lincoln, MA, United States 01773
Severus, Wolfram E., Badensche Strasse 7, D-10825 Berlin, GERMANY, FEDERAL REPUBLIC OF
PI US 6344482 B1 20020205
WO 9739759 19971030
AI US 1999-269361 19990322 (9)
WO 1997-US6712 19970423
19990322 PCT 371 date
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Choate, Hall & Stewart
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 387
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to a method of treating patients with **bipolar disorder** by administering omega-3 fatty acids.

TI Omega-3 fatty acids in the treatment of **bipolar disorder**

AB The present invention is directed to a method of treating patients with **bipolar disorder** by administering omega-3 fatty acids.

SUMM . . . to medical treatments for psychiatric disorders. More specifically, it is concerned with novel methods and compositions for treating patients with **bipolar disorder**.

SUMM Patients with **bipolar disorder** suffer recurrent, alternating cycles of mania and depression. In a controlled clinical study performed more than a decade ago, it. . .

SUMM . . . inhibit thrombosis and platelet aggregation and can lower blood pressure (see Dimmitt, Clin. Exp. Pharmacol. Physiol. 22:204-208 (1995)). Thus, the "**omega-3 phosphatidylcholines**" disclosed herein produce the same effects as lecithin in bipolar patients due to the release of free choline but reduce,. . .

SUMM In addition, the present invention is directed to a method of treating **bipolar disorder** using omega-3 fatty acids themselves, i.e. apart from phosphatidylcholine. These may be administered in a purified state, as part of. . .

SUMM Thus, a method has been developed for treating a human patient for **bipolar disorder** by administering omega-3 fatty acids at a dosage sufficient to reduce or eliminate the symptoms associated with the disorder, i.e.. . .

SUMM The present invention is also directed to an **omega-3 phosphatidylcholine**, useful in the treatment of **bipolar disorder**, consisting of glycerol esterified at both its α and β carbons to fatty acids. At least one, and preferably both,. . . phosphocholine. It is preferred that at least one of the esterified fatty acids be either eicosapentanoic acid or docosahexanoic acid. **Omega-3 phosphatidylcholines** with eicosapentanoic acid esterified to the α carbon and docosahexanoic acid esterified to the β carbon and vice versa are. . .

SUMM In another aspect, the present invention is directed to a pharmaceutical composition comprising one or more of the **omega-3 phosphatidylcholines** discussed above. The composition should contain sufficient triacylglycerol so that one or more unit doses provides enough agent to reduce or eliminate the symptoms associated with **bipolar disorder**. In some instances, lithium may be also incorporated into the composition in order to improve therapeutic effects.

SUMM The present invention is also directed to a method for treating **bipolar disorder** in a human patient by administering an omega-3 phosphatidyicholine. It is expected that this phosphatidylcholine will typically be administered at. . .

DETD **Bipolar disorder**: **Bipolar disorder** refers to a form of psychosis characterized by adnormally severe mood swings. The patient alternates between episodes of mania and. . .

DETD **Omega-3 phosphatidylcholine**: As used herein the term "**omega-3 phosphatidylcholine** " refers to a triacylglycerol in which the γ carbon of glycerol is esterified to phosphocholine, and at least one of. . .

DETD B. Method of Treating Patients For **Bipolar Disorder** Using Omega-3 Fatty Acids

DETD The present invention is directed to a method for treating human patients for **bipolar disorder** by administering omega-3 fatty acids. Although the method is not restricted to any one

particular type of omega-3 fatty acid,. . .

DETD . . . administered to a human patient should be at least the amount required to reduce or eliminate the symptoms associated with **bipolar disorder**. Specifically, the dosage should be high enough to either reduce the severity of the manic and depressive episodes experienced by. . .

DETD . . . patient and other clinically relevant factors. In many cases, a patient will already be taking medications for the treatment of **bipolar disorder** at the time that treatment with omega-3 fatty acid is initiated. In addition, patients may be taking medications for other. . .

DETD . . . composition containing one or more excipients or flavoring agents. Compositions may also include other active ingredients for the treatment of **bipolar disorder**, e.g. lithium. Preparations may be solid or liquid and take any of the pharmaceutical forms presently used in human medicine,. . .

DETD Omega-3 fatty acids may be used in combination with other agents effective at treating **bipolar disorder**, e.g. lithium or choline. These other agents may either be given together with omega-3 fatty acid in a single dosage. . .

DETD Individual preparations containing omega-3 fatty acid and other therapeutic agents for **bipolar disorder**, such as choline or lithium, may be provided in the form of a kit, comprising a carrier (e.g. a box. . . one or more components (bottles, vials, packets, etc.) in close confinement. Such a kit will be carried by patients with **bipolar disorder** and will typically contain written instructions concerning the way in which the enclosed drugs should be taken, potential side effects,. . .

DETD C. **Omega-3 Phosphatidylcholines**

DETD The present invention is also directed to **omega-3 phosphatidylcholines** in which glycerol is esterified at its γ carbon to phosphocholine and at least one of the fatty acids esterified. . .

DETD . . . standard techniques well known in the art, see e.g. U.S. Pat. No. 4,701,468. One suitable method is to synthesize the "**omega -3 phosphatidylcholines**" from commercially available precursor lyso-phosphatidylcholines. Specifically, a lyso-phos-phatidylcholine is acylated by combining the desired omega-3 fatty acid anhydride (e.g. from. . . catalyst (1.2 equivalents) in alcohol-free chloroform. Depending on the reaction conditions and the relative proportions of fatty acid, several different **omega-3 phosphatidylcholine** species will be generated. Using EPA and DHA, four major species will occur: dieicosapentanoylphosphatidylcholine, didocosahexanoylphosphatidylcholine, 1-eicosapentanoyl, 2-docosahexanoylphosphatidylcholine, and 1-docosahexanoyl, 2-eicosapentanoylphosphatidylcholine.. . .

DETD D. Method of Treating **Bipolar Disorder** Using **Omega-3 Phosphatidylcholines**

DETD The **omega-3 phosphatidylcholines** described above may be used for treating humans with **bipolar disorder** in the same manner and following the same procedures as those discussed in connection with **omega-3** fatty acids. The **phosphatidylcholines** may be given in a substantially purified form or as part of a pharmaceutical composition, It is expected that optimized dosages will have sufficient **omega -3 phosphatidylcholine** to deliver between about one and about 30 grams of free omega-3 fatty acid per day, with the

preferred daily. . .

DETD As with omega-3 fatty acids, the **omega-3 phosphatidylcholines** may be delivered by any route and are compatible with any dosage form. Oral dosage forms such as tablets, capsules,. . . included. It will be appreciated that one particularly attractive composition would include both a source of lithium as well as **omega-3 phosphatidylcholine**.

DETD In cases where parenteral administration is elected as the route of administration, preparations containing **omega-3 phosphatidylcholine**. may be provided to patients in combination with pharmaceutically acceptable sterile aqueous or non-aqueous solvents, suspensions or emulsions. Examples of. . .

DETD **Omega-3 phosphatidylcholine** and other agents useful in treating bipolar patients, preferably lithium or choline may be provided as separate components in the. . .

CLM What is claimed is:
1. A method of treating a human patient for **bipolar disorder**, comprising administering an omega-3 fatty acid to said patient at a dosage sufficient to reduce or eliminate the symptoms of. . .

IT 6217-54-5, Docosahexaenoic acid 10417-94-4, Eicosapentaenoic acid **87879-23-0 87879-27-4 98819-78-4 198779-10-1**
(ω-3 fatty acids and phosphatidylcholines for treatment of bipolar disorder)

References for Lithium to treat bipolar disorder


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=> d que
L15        2089 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "MENTAL DISORDER (L) BIPOLAR
                DISORDER"+OLD/CT
L27        1873 SEA FILE=HCAPLUS ABB=ON  PLU=ON  LITHIUM/CT(L)(BAC OR DMA OR
                PKT OR PAC OR THU)/RL
L28         303 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L27 AND L15
L29          22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND P/DT
L30         281 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 NOT L29
L31          77 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 NOT PY>1998
L32          20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND REVIEW/DT
L33          15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L32 AND LITH?/TI
L34           6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND BIPOL?/TI


=> d l34 ibib abs hitrnd 1-6

L34  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1998:740935  HCAPLUS
DOCUMENT NUMBER:          130:148033
TITLE:                    Glycogen synthase kinase-3 - a new target for
                          lithium's effects in bipolar
                          patients?
AUTHOR(S):                Agam, Galila; Levine, Joseph
CORPORATE SOURCE:         Faculty of Health Science, Ben-Gurion University,
                          Beersheva, Israel
SOURCE:                   Human Psychopharmacology (1998), 13(7), 463-465
                          CODEN: HUPSEC; ISSN: 0885-6222
PUBLISHER:                John Wiley & Sons Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 15 refs. on the possibility that lithium's therapeutic
     effect is mediated via inhibition of glycogen synthase kinase-3 in
     treatment of bipolar disorders.
CC   1-0 (Pharmacology)
IT   Mental disorder
        (manic bipolar disorder; glycogen
        synthase kinase-3 as new target for lithium's effects in bipolar human
        patients)
IT   7439-93-2, Lithium, biological studies
     RL: BAC (Biological activity or effector, except adverse); BSU
     (Biological study, unclassified); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (glycogen synthase kinase-3 as new target for lithium's effects in
        bipolar human patients)
REFERENCE COUNT:          15    THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34  ANSWER 2 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         1998:454808  HCAPLUS
DOCUMENT NUMBER:          129:197460
TITLE:                    Behavioral reversal of lithium effects by
                          four inositol isomers correlates perfectly with
                          biochemical effects on the PI cycle: depletion by
                          chronic lithium of brain inositol is
                          specific to hypothalamus, and inositol levels may be
                          abnormal in postmortem brain from bipolar
```

patients
AUTHOR(S): Belmaker, Robert H.; Agam, Galila; Van Calker, Dietrich; Richards, Mary H.; Kofman, Ora
CORPORATE SOURCE: Ministry of Health Mental Health Center, Faculty of Health Sciences Ben Gurion University of the Negev, Beersheva, Israel
SOURCE: Neuropsychopharmacology (1998), 19(3), 220-232
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 62 refs. The inositol depletion hypothesis of lithium (Li) action has been criticized, because depletion of inositol after chronic Li treatment has not been reproducible, effects of inositol to reverse Li-induced behaviors occurred also with epi-inositol, a unnatural isomer, and because inositol is ubiquitous in brain and hard to relate to the pathogenesis of affective disorder. Therefore, we review our studies showing that lithium depletion of brain inositol occurs chronically in the hypothalamus, a region not previously examined; that behavioral effects of four different inositol isomers including epi-inositol correlate perfectly with their biochem. effects; and that inositol in postmortem human brain is reduced by 25% in frontal cortex of bipolars and suicides as compared with controls. Because inositol in postmortem brain is reduced and not increased in bipolar patients, the relationship between inositol, lithium, and affective disorder is complex.
CC 1-0 (Pharmacology)
Section cross-reference(s): 14
IT **Mental disorder**
(**manic bipolar disorder**; lithium behavioral effects reversed by four inositol isomers in relation to biochem. effects on PI cycle in rat brain and inositol levels in postmortem bipolar humans)
IT **7439-93-2**, Lithium, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(lithium behavioral effects reversed by four inositol isomers in relation to biochem. effects on PI cycle in rat brain and inositol levels in postmortem bipolar humans)
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:454802 HCAPLUS
DOCUMENT NUMBER: 129:211123
TITLE: **Lithium**: a molecular transducer of mood-stabilization in the treatment of **bipolar** disorder
AUTHOR(S): Manji, Husseini K.; Lenox, Robert H.
CORPORATE SOURCE: Departments of Psychiatry and Behavioral Neurosciences, and Pharmacology, Molecular Pathophysiology Program, Wayne State University School of Medicine, Detroit, MI, USA
SOURCE: Neuropsychopharmacology (1998), 19(3), 161-166
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: English
AB A review with 42 refs. This article reviews data regarding the mechanism of action of lithium in bipolar disorder.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(**manic bipolar disorder**; lithium mol. mechanisms in mood-stabilization in treatment of humans with **bipolar disorder**)
IT **7439-93-2**, Lithium, biological studies
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(lithium mol. mechanisms in mood-stabilization in treatment of humans with bipolar disorder)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:305315 HCAPLUS
DOCUMENT NUMBER: 129:49066
TITLE: Recurrence risk in **bipolar** manic-depressive disorders after discontinuing **lithium** maintenance treatment: an overview
AUTHOR(S): Baldessarini, Ross J.; Tondo, Leonardo
CORPORATE SOURCE: Laboratories for Psychiatric Research, McLean Division of Massachusetts General Hospital, Harvard Medical School, Belmont, MA, USA
SOURCE: Clinical Drug Investigation (1998), 15(4), 337-351
CODEN: CDINFR; ISSN: 1173-2563
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 80 refs. Lithium remains unequaled in its research support as a standard maintenance treatment for bipolar manic-depressive disorders. It has important beneficial effects on recurring bipolar depression as well as mania, and in both types I and II bipolar syndromes, with powerful antisuicide effects not demonstrated with alternative mood-stabilizers. Numerous studies indicate that discontinuing lithium maintenance treatment is followed by sharply increased morbidity and possibly mortality, particularly in the 1st 6-12 mo. However, gradual discontinuation markedly reduces, and not merely delays, recurrences of mania or depression after discontinuing lithium, with an even stronger effect in bipolar type II than type I patients. Secondary long-term retreatment with lithium following discontinuation yields only minor average losses of benefits. Increased early recurrence risk may also arise after stopping long-term treatment with other neuropsychotropic drugs. Such reactions probably reflect physiol. adaptations of the brain to pharmacodynamic effects, and their impact may be limited by slow drug discontinuation. The phenomenon of high early post-treatment discontinuation recurrence risk has clin. and scientific implications for the design, management and interpretation of treatment protocols that involve discontinuing long-term treatments in disorders requiring maintenance pharmacotherapy with centrally neuropharmacol. active drugs.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(**manic bipolar disorder**; recurrence risk in bipolar manic-depressive disorders of humans after discontinuing

lithium maintenance treatment)
IT **7439-93-2**, Lithium, biological studies
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(recurrence risk in bipolar manic-depressive disorders of humans after discontinuing maintenance treatment with)
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:105090 HCAPLUS
DOCUMENT NUMBER: 128:212508
TITLE: Use of **lithium** in **bipolar** disorder
AUTHOR(S): Young, Robert C.
CORPORATE SOURCE: Department of Psychiatry, Westchester Division, The New York Hospital-Cornell Medical Center, White Plains, NY, USA
SOURCE: Medical Psychiatry (1998), 9(Geriatric Psychopharmacology), 259-272
CODEN: MEPSEN
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 52 refs. Somatic treatments that are effective for bipolar depression in younger patients can also be effective in the elderly. This chapter focuses on treatment of geriatric manic and depressed bipolar patients with lithium salts directed at acute suppression of symptoms, continuation treatment to prevent immediate relapse, and long term maintenance.
CC 1-0 (Pharmacology)
IT **Mental disorder**
(depression; lithium treatment of **bipolar disorder** in geriatric humans)
IT **Mental disorder**
(mania; lithium treatment of **bipolar disorder** in geriatric humans)
IT **Mental disorder**
(**manic bipolar disorder**; lithium treatment of **bipolar disorder** in geriatric humans)
IT **7439-93-2**, Lithium, biological studies
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(lithium treatment of bipolar disorder in geriatric humans)
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L34 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:88534 HCAPLUS
DOCUMENT NUMBER: 128:212458
TITLE: **Lithium** plus valproate as maintenance polypharmacy for patients with **bipolar** I disorder: a review
AUTHOR(S): Solomon, David A.; Keitner, Gabor I.; Ryan, Christine

E.; Miller, Ivan W.
CORPORATE SOURCE: Department of Psychiatry and Human Behavior, Rhode Island Hospital, Providence, RI, 02903, USA
SOURCE: Journal of Clinical Psychopharmacology (1998), 18(1), 38-49
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 99 refs. Standard pharmacotherapy for the maintenance treatment of patients with bipolar I disorder consists of lithium, valproate, or carbamazepine. However, many patients fail to respond to monotherapy with any of these agents, and as a result, psychiatrists often resort to polypharmacy. Findings from some open-label trials and retrospective chart reviews suggest this approach may be useful, but in the few controlled trials that have been conducted, the results have been neg. One drug combination that warrants further study as maintenance therapy is lithium plus valproate. Each is approved by the U.S. Food and Drug Administration for treatment of acute mania, and lithium has demonstrated efficacy for maintenance treatment as well. Some preliminary evidence suggests that the combination can be effective for patients who do not respond to monotherapy, and it seems to be no more dangerous than monotherapy. Concomitant administration of lithium plus. valproate does not significantly alter lithium pharmacokinetics, and statistically significant changes that arise in valproate pharmacokinetics are not clin. significant. Although it is not known whether the drugs interact to augment response, many of their effects in the central nervous system do differ, and there is no indication of pharmacodynamic interactions that oppose each other. Finally, some evidence suggests that lithium and valproate may differ with regard to clin. variables that predict response to treatment.

CC 1-0 (Pharmacology)

IT **Mental disorder**
(manic bipolar disorder;
Lithium/valproate maintenance polypharmacy for humans with bipolar I disorder)

IT 99-66-1 **7439-93-2**, Lithium, biological studies
RL: ADV (Adverse effect, including toxicity); **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(Lithium/valproate maintenance polypharmacy for humans with bipolar I disorder)

REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT